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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/777,838	02/12/2004	Mark K. Wedel	ISIC0008-100(FMDL0001US)	5903

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/777,838	WEDEL ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133) Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-28-04 and 11-30-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Pending Claims

Claims 1-8 are pending and currently under examination.

Information Disclosure Statement

The information disclosure statement filed October 28, 2004 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each document listed that is not in the English language. Accordingly, Citation NOs. B13 and B30 have been placed in the application file, but the information referred to therein, has not been considered.

Specification

The disclosure is objected to because of the following informalities: Page 95, line 21 reads, "Patients elf-administered 240mg". It appears that "elf-administered" is a typographical error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and /or chemical properties, functional characteristics, structure/function correlation, or any combination thereof.

The claims are drawn to methods of treating pouchitis in a human comprising administering an oligonucleotide targeted to human ICAM-1 mRNA.

Given the broadest reasonable interpretation of the claims consistent with the specification, the "oligonucleotide" recited in the claims refers to an oligomer or polymer of ribonucleic acid or deoxyribonucleic acid. See page 16 of the instant specification. As broadly written, the term "oligonucleotide" reads on antisense oligonucleotides, siRNA molecules, triplex molecules, aptamers, ribozymes, DNAzymes, and any RNA or DNA oligomers. Although the instant specification provides enabled working examples for an antisense oligonucleotide (identified as ISIS 2302 or SEQ ID NO:1), the antisense oligonucleotide is not a representative sample of the genus of the term "oligonucleotide". Accordingly, one skilled in the art cannot determine whether the inventor was in possession of the invention of "any type of oligonucleotides targeted to human ICAM-1 mRNA" as claimed in the broad claim, claim 1 and its dependent claims 2-8.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991), which clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (see page 1117).

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating pouchitis in a human in need thereof comprising administering a pharmaceutical composition comprising an antisense oligonucleotide of SEQ ID NO:1 that is 20 nucleotides in length, further comprising a pharmaceutical excipient, hydroxypropylmethylcellulose, in an enema formulation, does not reasonably provide enablement for a method of treating pouchitis in a human in need thereof comprising any other formulations or any other nucleic acid compositions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient

evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In the instant case, the specification provides clinical assessment data for the methods of treating human patients with pouchitis comprising administering a pharmaceutical composition known as ISIS-2302 comprising the instant SEQ ID NO:1 and a pharmaceutically acceptable carrier, hydroxypropylmethylcellulose in an edema formulation. See Example 17. As neither antisense therapeutics nor clinical trials are performed routinely in the art, to determine whether pharmaceutical compositions comprising any oligonucleotides targeted to any portion of the human ICAM-1 mRNA sequence, further comprising any type of penetration enhancer would effectively treat pouchitis in a human patient would require undue experimentation. The unpredictable therapeutic effects of DNA-based drugs for human use are addressed by Patil et al's comprehensive review (*The AAPS Journal,* 2005, 7:E61-E77).

On page E62, Patil et al. teach the complications of using DNA-based drugs as following:

"The innate ability of DNA-based drugs to be internalized by target cells is minimal under normal circumstances. In addition, poor biological stability and a short half-life result in unpredictable pharmacokinetics. Furthermore, DNA molecules that do manage to enter the cell are subsequently subjected to intracellular degradation along with stringently restricted nuclear access. The resulting random delivery profile of DNA-based drugs is further complicated by a lack of in vivo/in vitro correlation of their pharmacological outcomes."

As such, one of ordinary skill in the art would not be able to predict the therapeutic outcomes of oligonucleotides targeted to ICAM-1 mRNA sequence in the absence of clinical data. The unpredictable pharmacokinetics of DNA-based drugs as taught by Patil et al. thus would necessitate undue experimentation for one skilled in the art to ascertain the "pharmacological outcomes" of the claimed oligonucleotide targeted to ICAM-1 mRNA for the treatment of pouchitis in a human patient.

Patil et al. further teach the significance related to the optimal length for oligonucleotides with efficient antisense activity (page E65). Thus, it would be highly unpredictable whether an oligonucleotide comprising at least an 8 nucleobase portion of SEQ ID NO:1 would result in the consistent or commensurate pharmacokinetics as the 20-mer ISIS-2302 exemplified in the specification.

Given the unpredictable nature of DNA-based drugs *in vivo* and the lack of specific guidance to practice the method of treating pouchitis in human patients by administering any other pharmaceutical compositions than the instantly tested ISIS-2302, one of ordinary skill cannot practice the instant invention without undue experimentation testing the pharmaceutical effects of oligonucleotides other than ISIS-2302. Further, the instant specification does not provide any working examples for a pharmaceutical composition comprising an oligonucleotide and a penetration enhancer. Although increased *in vivo* bioavailability of oligonucleotide compositions further comprising a penetration enhancer is demonstrated in the instant specification, this demonstration is shown in healthy rats not in human patients suffering from pouchitis. Again, due to the unpredictable nature of DNA-based drugs as taught by Patil et al.,

one skilled in the art cannot extrapolate the improved pharmacological effects of the ICAM-1 oligonucleotide compositions merely based on healthy rat model studies.

In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), the Court ruled that a rejection under 35 U.S.C. 112, first paragraph for lack of enablement was appropriate given the relatively incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims. One skilled in the art cannot predict that the claimed method of treating pouchitis in a human patient will be effective, if other than ISIS-2302 compound comprising hydroxypropylmethylcellulose in an edema formulation was administered to the patient, particularly since the specification has not set forth any other compositions that are capable of treating pouchitis required by claims 1-8. It is well known that the art of nucleic acid-based drug discovery for therapy is highly unpredictable as stated above. It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method drawn to treating pouchitis would be used without undue experimentation.

Accordingly, claims 1-8 are only enabled for the method of treating pouchitis in a human in need thereof, comprising administering ISIS-2302 further comprising hydroxypropylmethylcellulose in an edema formulation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As broadly written, the instant claims read on any ICAM-1 mRNA sequence. Although it is specified that the ICAM-1 mRNA sequence be the human mRNA sequence, it is art-recognized knowledge that there are a number of different mRNA splice variants or isoforms for a particular gene due to differently spliced post-transcriptional processing of the gene sequence. Therefore, it is unclear which ICAM-1 mRNA sequence is targeted by the instantly claimed pharmaceutical composition comprising an oligonucleotide. Since there is no positive recitation of the SEQ ID NO specified for the required human ICAM-1 mRNA sequence in the broad claim, claim 1, line 4, the recited pharmaceutical composition comprising an oligonucleotide targeted to human ICAM-1 mRNA is considered arbitrary and ambiguous. Accordingly, one of ordinary skill in the art would not be able to ascertain the recited mRNA sequence due to the indefinite claim language as state above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-3 of U.S. Patent No. 6,169,079 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of claims 2-3 of U.S. Patent No. 6,169,079 B1 embraces the patent protection sought by the scope of the instant claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday. from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635